

# Neuropsychological alterations by chronic exposure to low concentrations of carbon monoxide in highway workers of Mexico

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Original article

## ABSTRACT

### Background

Workers in the automobile industry, service stations, and those working in the streets are in chronic contact with low concentrations of carbon monoxide and at risk of damaging their cardiovascular, hematological, and nervous systems.

### Objective

Identify erythrocytosis and neuropsychological alterations in highway workers chronically exposed to low concentrations of CO.

### Method

Cross-sectional study that included 72 workers in Mexico-Puebla Highway booths; 60 cashiers and 12 shift managers, in which sociodemographic, clinical, and occupational variables were explored. Hemoglobin (Hb), hematocrit (Htc) and carboxyhemoglobin (COHb) were determined in their blood, and the *Carbon monoxide neuropsychological screening battery* (CONSB) was applied. The workers in charge of the shift were the group less exposed to CO, while the cashiers would form the group with greater exposure.

### Results

In 49 workers, Hb:  $18.1 \pm 1.9$  mg/dL and Htc:  $55.3 \pm 8.7$  without significant differences between groups ( $p = 0.82$ ). Greater alteration was identified in the exposed group in the digit symbol test ( $p = 0.012$ ), trail-making part B ( $p = 0.002$ ), and digit span ( $p = 0.003$ ); the construction blocks test result was borderline ( $p = 0.07$ ).

### Discussion and conclusion

The group with the highest exposure to CO had poorer performance in visual perception, encoding, visual-motor perception, and immediate memory. Therefore, it is important to consider epidemiological surveillance workers who can intervene in cases with abnormal tests. The innocuous perception of chronic exposure to CO in these workers must be avoided.

**Key Words:** Neuropsychological alterations, carboxyhemoglobin, CONSB, chronic occupational exposure, carbon monoxide.

## RESUMEN

### Antecedentes

Trabajadores de la industria automovilística, estaciones de servicio, autopistas de peaje, estacionamientos y los que laboran en las calles, están en contacto crónico con bajas concentraciones de monóxido de carbono (CO) y, por lo tanto, en riesgo de sufrir alteraciones en los sistemas cardiovascular, hematológico y nervioso.

### Objetivo

Identificar la relación de las alteraciones neuropsicológicas con la exposición crónica a bajas concentraciones de CO, en trabajadores de autopistas de peaje.

### Método

Estudio transversal en 72 trabajadores de autopistas de peaje de la carretera México-Puebla; 60 cajeros y 12 encargados de turno. Se exploraron variables socio-demográficas, clínicas y ocupacionales, y se determinó hemoglobina (Hb), hematocrito (Htc) y carboxihemoglobina (COHb) en sangre. Se aplicaron pruebas neuropsicológicas (*Carbon monoxide neuropsychological screening battery* CONSB). Los encargados de turno conformaron el grupo menos expuesto y los cajeros el de mayor exposición a CO.

### Resultados

En 49 trabajadores, Hb:  $18.1 \pm 1.9$  mg/dL y Htc:  $55.3 \pm 8.7$ , sin diferencias significativas entre grupos ( $p = 0.82$ ). Se observó menor desempeño en el grupo más expuesto, en el test de dígitos y símbolos ( $p = 0.012$ ), senderos B ( $p = 0.002$ ) y dígitos ( $p = 0.003$ ). El test de construcción con bloques resultó limítrofe ( $p = 0.07$ ).

### Discusión y conclusión

El grupo de mayor exposición al CO tuvo menor desempeño en percepción visual, codificación, percepción visomotora y memoria inmediata. Por ello, consideramos importante realizar vigilancia epidemiológica en los trabajadores, para intervenir en los casos con alteraciones en las pruebas. Asimismo, se debe evitar la percepción de que la exposición crónica al CO en estos trabajadores es inocua.

**Palabras clave:** Alteraciones neuropsicológicas, carboxihemoglobina, CONSB, exposición crónica ocupacional, monóxido de carbono.

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## BACKGROUND

As well as having an endogenous source of carbon monoxide (CO), human beings are also exogenically exposed to this compound. There are multiple sources of this: motor vehicles, heating equipment, ovens, and cigarette smoke, among others.<sup>1</sup> CO passes into the lungs and is easily absorbed by the circulatory system, as it already has around 220 times more affinity with hemoglobin than oxygen. Its negative effects are union with Hb to form carboxyhemoglobin (COHb), which causes blockage in the transport of oxygen<sup>2</sup> and also its union with proteins, mostly myoglobin, thereby forming carboxymyoglobin which is found in the heart and musculoskeletal system. Furthermore, it produces direct cellular damage when joining with cytochrome  $\alpha 3$  with the subsequent blocking of the respiratory chain and reduced production of ATP, which favors anaerobic metabolism, lactic acidosis, and cellular death by producing non-ischemic hypoxia.<sup>3</sup>

Chronic exposure to CO shows a systemic compensatory process of response to hypoxia, which includes erythrocytosis, hypervolemia, and cardiomegaly.<sup>4</sup> In the workplace, blood tests on a heterogeneous sample of workers at a passenger terminal with various ages and work schedules showed considerable levels of COHb, accompanied by alterations in the speed of glomerular sedimentation rate (GSR), hemoglobin (Hb), Lactate dehydrogenase (LDH), myocardic creatine kinase (CKmb), and ultra-sensitive C-reactive protein (us-CRP).<sup>5</sup>

On the other hand, it has been shown that prolonged exposure to low concentrations of CO –from days to months– can have subtle effects on various structures of the central nervous system. CO activates polymorphonuclear leukocytes, which perform diapedesis and cause peroxidation of cerebral lipids, particularly in the globus pallidus, which is very rich in iron.<sup>6</sup> Furthermore, anoxia produces neuro-toxicity due to the mass release of neurotransmitters such as glutamate and the reduction of dopaminergic neurons which causes low levels of dopamine and may explain psychiatric effects.<sup>7</sup>

Other studies report that brain damage can be generalized, although the striatum seems to be particularly vulnerable, probably due to the fact that parts of it are at the limit of irrigation by the anterior and middle cerebral arteries.<sup>8</sup> Other sensitive areas are the basal ganglia, cerebellum, and peri-ventricular white matter, as well as the semiovale, an area which is generally significantly related to brain sequelae.<sup>9</sup>

There are studies on the chronic effect of CO exposure on neuropsychological functions, but they deal with cases of accidental contact with combustion apparatus such as dilapidated heaters or stoves. One study presents seven cases with exposure of up to three years, but only one reported the level of exposure (400 ppm). This referred to

symptoms caused by chronic exposure to CO such as fatigue, headaches, fever, pharyngeal pain, nausea, diarrhea, palpitations, sleep disorders, weight loss, tinnitus, chest pain, irritability, and emotional changes such as emotional lability and severe depression. Psychological tests observed reduction in spatial orientation, slowing of motor skills, and a marked deterioration in memory.<sup>10</sup>

One interesting case is that of a 45 year-old woman with accidental CO exposure for a year, during which she experienced problems with balance, headaches, asthenia, hypoacusia, inability to speak clearly or produce a complete sentence, irritability, and face pain. Magnetic resonance imaging of the brain was carried out 15 months after the exposure, which revealed multiple bilateral lesions in the basal ganglions (more severe in the globus pallidus than the putamen). Neuropsychological tests were carried out after 17 months, which showed that learning and recovering new information were primarily altered; results which suggest a subtle dysfunction in the frontal lobe associated with subcortical injury. Another psychological assessment was carried out 29 months after the exposure, and results for the patient were found to be lower than expected, primarily in memory and verbal reasoning tasks.<sup>11</sup>

## OBJECTIVE

In Mexico, highway tollbooth workers are chronically exposed to unknown concentrations of CO, mostly generated from motor vehicles. This risk group has not been studied before; as such, the aim of the present study is to determine the relationship between CO exposure and neuropsychological alterations in these workers.

## METHOD

A cross-sectional study was carried out between November and December 2012 on 72 workers of both sexes: 60 were cashiers working on toll booths and 12 were shift managers. None of those examined advised having any hematological or neurological illnesses which would lead to their exclusion from the study. The sample was by convenience; in other words, those who wanted to participate and agreed to sign an informed consent form. They were given a standardized questionnaire, which collected information about age, birthplace, education, working history with exposure to carbon monoxide (CO), current job, time in current job, time travelling to work, type of transport used, history of contact with pneumotoxins such as wood and coal smoke, as well as exposure at work, history of chronic illnesses, smoking, and/or alcohol consumption. It explored symptoms related to acute CO poisoning at the time of the interview, and this was positive if it happened more than once a week.

## Blood samples

Some 68% (49) of the workers agreed to a blood test being taken during rest days or prior to starting their work shift, with the aim of determining hemoglobin (Hb), hematocrit (Hcto), and carboxyhemoglobin (COHb), by means of conventional hematic biometry. For erythrocytosis, the cutoff point for Hcto was established as >51% for men and >48% for women.<sup>12</sup> The determination of COHb in blood was by colorimetry with the Katsumata method in total, non-hemolyzed venous blood, collected in EDTA tubes. A value for COHb of >5% was considered acute intoxication.<sup>13</sup> These studies were carried out at the Ruiz Clinic, located in the State of Puebla, which has Bureau Veritas certification ISO 9001:2010.

## Neuropsychological tests

To assess the neuropsychological alterations, a specific battery was used for CO exposure, called the *Carbon monoxide neuropsychological screening battery* (CONSB), which has six questions. The first is the auditory verbal learning test by Rey, which assesses short- and medium-term memory through repetition of 15 words in five attempts.<sup>14</sup> The following test is retention of digits, which assesses immediate memory through repetition of a series of numbers in direct and reverse order. The third is the digit and symbols test, which assesses visual perception and codification. In this test, the subject must correctly associate the highest quantity of numbers with their corresponding symbol within 90 seconds. The fourth is a trail-making test which is subdivided into type A and type B. The first consists of an ascending union of numbers, and the second is numbers and letters. Both assess visuo-motor perception.<sup>15</sup> The penultimate test is Wechsler's visual memory test, in which a geometric figure is observed for ten seconds, to then be drawn and immediate visual memory assessed. Finally, the sixth test is the cubes test, which assesses abstract visual processing and problem solving through the construction of designs with the use of colored cubes.<sup>16</sup> Furthermore, all workers were asked whether they were tired, or had ingested alcohol or stimulants prior to starting the tests.

## Statistical analysis

Data from the questionnaire, the CONSB, and the laboratory tests was captured on Excel and analyzed using the statistical software Stata.SE 12.0. A univariate and bivariate analysis took place, as well as differences in means and proportions with the student's t and the chi<sup>2</sup> test, respectively.

## Assigning exposure

The toll booth business studied carried out an environmental monitoring of CO in 2006, in the area of vehicular in-

flux which reported a maximum concentration of 2ppm, the same as that established in the NOM-021-SSA1-1993 (11.00 ppm is equivalent to 12,595 µg/m<sup>3</sup> on a mobile average of eight hours once a year).<sup>17</sup> The working conditions have not substantially varied from the time when this monitoring was carried out.

Due to the nature of the activities carried out, there is a greater likelihood that the cashiers will be chronically exposed to low concentrations of CO, as they are located in the middle of the highway where traffic passes, in booths which only have the natural ventilation of the air outside, and which are located close to where engine fumes are emitted from motor vehicles. These workers charge the drivers their toll for an eight hour shift, with an average flow of 800 - 2,000 vehicles per shift for each worker, which is why this group was designated as having the greatest exposure. The shift managers for the booths were considered to have the least exposure, as they were not in contact with the traffic, and therefore the exhaust fumes. Their main activity is administrative, although they do also work an eight hour shift each day. Both groups have a half hour meal break and two rest days per week.

## RESULTS

Of the 72 workers interviewed, 93% (67) were men. The average age was 43.4±8.5 years, and the minimum level of education was secondary. Some 10% (7) of the sample studied had Type 2 diabetes mellitus, with an average of 13 years' development of the illness, and a range of one to 30 years. Furthermore, 6% (4) advised having arterial hypertension, with an average of 2.5 years' development, and a range between one and ten years. In terms of their jobs, 83% (60) of the participants were cashiers and 17% (12) were shift managers. Of all the participants, 18% (13) had a history of previous occupational exposure to CO, mostly as land transport drivers (Table 1).

The presence of acute intoxication symptoms due to CO exposure was outstanding, especially eye irritation (81% vs. 50%), fatigue (75% vs. 66%), drowsiness (76% vs. 58%), and headaches (56% vs. 58%) in the workers with the greatest exposure, although the difference was not statistically significant (Table 2).

Some 47% (23) had erythrocytosis, with Hb of 18.1 ± 1.9 mg/dL and Hcto of 55.3 ± 8.7, with no significant difference between exposure groups ( $p = 0.82$ ). Furthermore, figures for COHb of 5.7±2.4% were found in 70% of the samples, compatible with acute intoxication, also without significant difference. In terms of the neuropsychological tests, more alteration was found in the most exposed group in the digits and symbols test ( $p = 0.001$ ), trails B ( $p = 0.002$ ), and the digits test ( $p = 0.003$ ). The block construction test was shown as borderline ( $p = 0.07$ ). In all of the tests with the exception

**Table 1.** Sociodemographic characteristics of 72 highway toll booth workers in 2012

	N	Mean (SD)	Range
Age			
Managers	12	47.3 (12.1)	33 a 66
Cashiers	60	43.0 (9.3)	25 a 85
Time in job			
Managers	12	11.2 (6.9)	1 a 20
Cashiers	60	11.7 (5.9)	2 a 28
	Categories	N	Percentage
Sex	Women	5	6.9
	Men	67	93.1
Education	Secondary	15	20.8
	Technical school	9	12.5
	High school	26	36.1
	Bachelor's	22	30.6
Chronic illnesses	Diabetes mellitus	7	9.7
	Hypertension	4	5.5
	Others	6	8.3
Exposure to pneumotoxins (wood and/or coal)	Positive	22	30.6
	Negative	50	69.4
Smoking (smoking index)	SI>5	4	5.6
	SI<5	7	9.7
	Denied	61	84.7
Alcohol consumption	≥1 time per week	3	4.2
	<1 time per week	26	36.1
	Denied	43	59.7
Journey time to work (minutes)	<30 minutes	23	31.9
	30 a 60 minutes	30	41.7
	61 a 120 minutes	12	16.7
	121 a 240 minutes	7	9.7

SI: Smoking index.

of Rey's learning test, those least exposed showed the better performance. As such, in the digits retention, symbols and digits, trails b, Wechsler's visual memory test, and the block construction test, the differences in means was significant (Table 3).

**Table 2.** Prevalence of symptoms of acute carbon monoxide intoxication related to job, in highway booth workers in 2012

Symptom	Those least exposed: Those most exposed:		p
	managers n (%)	cashiers n (%)	
Headache	7 (58)	34 (56)	0.91
Fatigue	8 (66)	45 (75)	0.55
Runny nose	4 (33)	12 (20)	0.31
Nasal irritation	6 (50)	28 (46)	0.83
Nausea	1 (8)	17 (28)	0.14
Eye irritation	6 (50)	49 (81)	0.01
Drowsiness	7 (58)	46 (76)	0.19
Coughing	1 (8)	12 (20)	0.34
Dyspnea	2 (16)	11 (18)	0.89
Abdominal pain	0 (0)	5 (8)	0.30
Tachycardia	2 (16)	17 (28)	0.40
Angina	3 (25)	13 (21)	0.80

## DISCUSSION AND CONCLUSION

The workers in this study showed greater intensity and frequency of symptomatology of acute intoxication by CO, in comparison to that reported by Chávez et al. (2005) and Rojas et al. (2001). The studies mentioned analyzed workers who verified motor vehicles, and kiosk workers who also have close contact with CO emissions of up to 8ppm, and work up to 12 hours,<sup>18,\*</sup> in comparison with the 2ppm of CO recorded in the previous environmental monitoring check carried out in 2006 on the toll booths in the present study. These figures are within the norm established internationally by the Environmental Protection Agency (EPA), which allows a maximum of 10 (mg/m<sup>3</sup>), equivalent to 9ppm/volume of CO in the air in an average of eight hours, and of 35 ppm in a maximum of one hour. The *Occupational Safety and Health Administration* (OSHA) also establishes 55 mg/m<sup>3</sup> (50ppm) maximum carbon monoxide in the air as an av-

\* General Management of Costa Rica Transport Police. Assessment of exposure to carbon monoxide of workers at the verification center for gas, smoke, and noise tests. 2005.

**Table 3.** Presence of neuropsychological alterations, different means of performance in tests, and laboratory results in highway toll booth workers in 2012

Test	Normal value	Job	n	Subjects with alteration (%)	p	Mean (SD)	p
Rey's learning test	>48	Managers	12	2 (17)	0.530	41.2 (5.3)	0.380
		Cashiers	60	15 (25)		41.9 (7.2)	
Digit retention	>4	Managers	12	0 (0)	0.003	6.5 (1.3)	0.0010
		Cashiers	60	27 (45)		4.9 (1.6)	
Digits and symbols	>47	Managers	12	0 (0)	0.012	50.2 (7.1)	0.0013
		Cashiers	60	22 (37)		43.2 (7.0)	
Trails A	<31	Managers	12	4 (33)	0.590	32.6 (9.5)	0.200
		Cashiers	60	25 (42)		34.6 (10.3)	
Trails B	<97	Managers	12	0 (0)	0.002	64.5 (13.9)	0.007
		Cashiers	60	28 (47)		80.8 (21.6)	
Wechsler's visual memory test	>7	Managers	12	2 (17)	0.290	8.1 (1.1)	0.080
		Cashiers	60	19 (32)		6.9 (1.5)	
Block construction test	>36	Managers	12	7 (58)	0.010	30.9 (2.6)	0.010
		Cashiers	60	49 (82)		23.7 (1.2)	
Hemoglobin		Managers	10	—	—	17.3 (1.5)	0.260
		Cashiers	39			17.0	
Hematocrit	<51%	Managers	10	5 (50)	0.820	51.8 (5.6)	0.240
		Cashiers	39	18 (46)		50.4	
Carboxyhemoglobin	<5%	Managers	10	7 (70)	0.960	5.9 (2.4)	0.380
		Cashiers	39	27 (69)		5.6	

erage during a work shift of eight hours.\* The bibliography mentions symptoms of acute intoxication according to CO concentration levels, which causes reduction in the perception of stimulants and reduced working capacity when there is exposure to 4 to 6ppm of CO; to present headaches and/or abnormal vision it must be 10ppm.<sup>19</sup> In the present study, the workers referred to eye irritation, fatigue, drowsiness, and headaches, in which other factors may intervene such as contact with suspended particles of hydrocarbons and other contaminants produced by gasoline or diesel combustion, such as sulfur dioxide and nitrogen oxide,<sup>20</sup> and the workers also working extended shifts. Although solvent spillages have been reported close to the booths, especially of fuels, these are usually in small quantities and are immediately controlled by the cleaning team due to the risk of inflammation, which negates it being considered a determining factor.

In all tests except the Rey learning test, the group with the least CO exposure had the best performance. Significantly worse performance was also observed in visual perception, visuo-motor, immediate memory, and immediate visual memory in the toll booth cashiers. Despite the results in various studies being similar, no specific distinctive pattern has been found for the deficits in neuropsychological tests. On the one hand, this is because different types of populations have been explored, at variable concentrations and

periods of CO exposure, but especially because there is a wide variety of neuropsychological and specific tests utilized, without there being a standard battery to assess patients or subjects, which makes comparison between studies difficult. For example, Myert et al. (1998) described a series of alterations including memory, poor visuo-spatial functioning, the executive system, depression, problems with abstraction, fine manual motor control, attention, speed of cognitive processing, and other non-specific psychiatric symptoms.

A study carried out by Amitai in 1998 had greater similarities with the present study, as it compared students (average age of 22), 45 of whom were exposed to low concentrations of CO (17 - 100 ppm) from kerosene heaters and 47 who were not, for a period of 1.5 to 2.5 hours. The CONSB was applied and the same tests were found to be altered as in the present study, as well as the design with blocks and as such, temporal-spatial orientation. These alterations were shown in spite of the level of COHb exposure levels being very low (0.01 to 0.11%); this indicates the vulnerability of the brain and cognitive functions to hypoxia-ischemic changes.<sup>21</sup> They also show the vulnerability of the mechanisms independent of the COHb levels which cause these changes, as shown in the improvement of patients who have treatments in hyperbaric chambers, who present almost normal levels of COHb before the session, but who show a significant improvement in neuropsychological tests after the therapy.<sup>22</sup>

The tests which were altered in the present study showed a tendency to negatively influence visual function; this had already been found by Yona in 1998 in acute ex-

\* Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for Carbon Monoxide. Atlanta, 2012.

posures. From 1970, Mikulka reported alterations in the superior centers of the Central Nervous System in people with COHb levels between 2% and 10%, who presented a level of alteration in their mental functions. It primarily affected their visual discrimination, estimation of time, and then caused difficulties in fine coordination of limbs and the performance of complex tasks.<sup>23</sup> That might explain why in this study, there was low performance in the most exposed workers –in the test with construction blocks– but without it reaching significant differences between groups. Perhaps the damage to these capacities would be greater and more evident with greater chronicity. Furthermore, in the workers studied, there was the possibility that afferences with the pre-central area –specifically Brodmann area 8, responsible for coordination of ocular movement– were involved (Román Lapuente, 2010).

Generally, and in spite of not having found significant changes in terms of erythrocytosis and acute intoxication due to CO in terms of work, it is important to follow up in this regard in all the workers involved here. No prevalence of erythrocytosis was found in the population in general, however, the hematological changes found in 47% of the workers is far from the 9% of secondary erythrocytosis reported in patients with COPD,<sup>24</sup> despite the second having serious repercussions on oxygenation. Faced with these facts, there is the possibility that chronic exposure to low concentrations of CO is an important factor in the high prevalence of erythrocytosis, in spite of no study having been identified that establishes, finds, or disproves this association.

Some 70% of workers in both groups presented COHb figures over 5%, which surpasses the tolerable limits established by the *American Conference of Governmental Industrial Hygienists* in 2002: 3.5% at the end of the shift, and that of the *National Institute for Occupational Safety and Health* (NIOSH), of 5%.\* These results do not agree with what was expected for an exposure to 2ppm of CO, which is the concentration obtained during the last environmental check on toll booths in 2006, which could not be updated due to lack of resources, and which has probably increased in recent years due to the increase of vehicle traffic on toll roads, due to which it should be carried out once again.

For now, it is vital to take preventative measures for deep vein thrombosis or pulmonary embolism, consequences expected in patients with erythrocytosis. In this sense, prolonged normobaric oxygen therapy and hyperbaric oxygen therapy (HBOT) would be suggested, which have shown improvements in the most common symptoms of chronic CO intoxication. While this therapy is applied, it would be recommended to administer vitamin C to tackle free radicals formed by oxidative metabolism.<sup>25</sup> As well as

helping with hematological effects, such therapy improves neuropsychological functions. Although it has not been assessed in human beings, the mechanism includes the preservations of the production of ATP as a modulator of ischemia reperfusion, and the prevention of peroxidation of lipids at a cerebral level.<sup>26</sup> After the use of the therapy, the symptoms of acute CO intoxication, neuropsychological tests, and blood concentrations of COHb and Hb could be assessed, in order to better analyze the participation of CO in the appearance of such alterations.

## Limitations of the study

Within the limitations of this study is having studied a small and convenient sample - a situation which is common in studies of an occupational nature. The presence of a bias in the surveyor is likely in the neuropsychological tests, which was reduced as much as possible, in that the surveyor did not know the job of each worker. The lack of major financial resources was another obstacle which impeded carrying out environmental monitoring and increasing the number of participants to undertake the blood test. On the other hand, in this particular working environment, it is very likely that as well as CO, there is a wide range of other contaminants and suspended particles to which the workers are exposed, and which may have a role in producing the effects found in the tests carried out in the sample of workers.

The scientific literature does not clearly define the phenomenon of chronic CO intoxication, nor does it determine the time or atmospheric concentration for it to be considered as such. Because of this, it was not possible to determine whether the results obtained are directly caused by exposure to CO; however, it was possible to establish evidence of poorer performance in workers exposed to low concentrations of CO, and with COHb levels greater than those allowed. As such, it is imperative to avoid the perception that this gas is innocuous, even at low concentrations; this implies the importance of carrying out environmental monitoring within a formal program of epidemiological monitoring which includes preventative and therapeutic medical follow-up in these types of workers.

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## Conflict of Interest

The authors do not declare any conflicts of interest.

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\* ACGIH (American Conference of Governmental Industrial Hygienists) Carbon Monoxide: TLV Chemical Substances. Ohio, 2001.

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